IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Anthony Jevnikar et al.

Application No.: 10/005,073

Filed: December 7, 2001

For: METHODS AND PRODUCTS FOR CONTROLLING THE IMMUNE RESPONSES IN MAMMALS

Mail Stop AF

Group Art Unit: 1644

Examiner: GERALD R EWOLDT

Confirmation No.: 8806

PRE-APPEAL BRIEF REQUEST FOR REVIEW
PURSUANT TO 1296 OG 67 AND 1303 OG 21

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Review of the final rejections of claims 52-59-61, 63, 69-91 and 95 in the above captioned application under the Pre-Appeal Brief Conference Pilot Program described at 1296 OG 67 and at 1303 OG 21 is respectfully requested.

Claims 52-101 are pending in the application. Claims 53-58, 62, 64-68, 92-94 and 96-101 have been withdrawn from consideration. Claims 52, 59-61, 63, 69-91 and 95 have been acted upon and the final rejections thereof have been appealed to the Board of Patent Appeals and Interferences by Notice of Appeal submitted concurrently herewith. The appealed claims appear in Appendix A.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 52-59-61, 63, 69-91 and 95 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to enable a person of skill in the art to make and/or use the claimed invention. The alleged basis of the rejection is set forth in the Office Action mailed February 10, 2004 and restated in the Office Actions mailed October 8, 2004, April 19, 2005, and October 18, 2006.

The Office bases the rejection on the allegation, which has been sufficiently refuted by Applicants, that "Whereas tolerance has been repeatedly induced in mice, the identical/equivalent

methods have not worked in humans." OFFICE ACTION mailed 10/08/2004 at 2. Even if the allegation were true, the Federal Circuit has recognized that "[t]he mere fact that something has not previously been done clearly is not [] a sufficient basis for rejecting all applications purporting to disclose how to do it." *Gould v. Quigg*, 3 U.S.P.Q. 2d 1302, 1304 (Fed. Cir. 1987).

Applicants have provided more than sufficient documentary and testimonial evidence to refute the allegations made by the Office in support of the rejection. In particular, Dr. Jevnikar has submitted declarations. (Attachments to the Replies filed July 12, 2004 and February 8, 2005.) Dr. Jevnikar's declarations are supported by evidence published in peer reviewed journals that oral tolerance has been achieved in humans by Husby et al., *Journal of Immunology*, 152:4663-70, 1994 and McKown et al., *Arthritis and Rheumatism*, 43:1054-61, 2000. (Exhibits A and B attached to the Declaration of Dr. Jevnikar filed February 8, 2005) A declaration or affidavit is, itself, evidence that must be considered. M.P.E.P. § 2164.05.

The determination of enablement should always be based on the weight of all the evidence. *Id.* "The examiner should **never** make the determination based on personal opinion." *Id.* (emphasis in original). Applicants have submitted direct *in vivo* evidence of the enablement of the method in an art accepted animal model. "[P]roof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995). Furthermore, evidence provided by an applicant needs to be merely convincing to one skilled in the art. M.P.E.P. § 2164.05.

The Office has relied upon a trade paper report of the cessation of a clinical trial as evidence of non-enablement. OFFICE ACTION mailed 2/10/2004, at 3 (citing *Marketletter* (1999)). The *Marketletter* is a newspaper that provides business information in order that interested persons can decide whether it is a good time to buy the stock of a particular pharmaceutical company. Applicants respectfully submit that an article about a business decision in a business journal does not provide a credible basis for rejecting the enablement of a patent application that is supported by data and evidence.

Even if the *Marketletter* were a credible source of scientific information, the article would not support the Office's allegation. The *Marketletter* article does not state that testing of Colloral was stopped not because of it was harmful or because it had no effect, but only because the statistical results did not warrant further spending on late clinical trials. The *Marketletter* is reporting a business decision, not a scientific conclusion, and not even a determination of effectiveness by the FDA. But even an actual regulatory determination would not support the Office. The Federal Circuit has cautioned the PTO not to "confuse[] the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana*, 34 USPQ2d 1437, 1442 (Fed. Cir. 1995).

The Office has relied upon Goodnow, *The Lancet*, 357:2115-20, 2001, but the portion of Goodnow relied upon by the Office is actually stating a conclusion regarding the action of corticosteroids. By contrast, with respect to oral tolerance Goodnow states on page 2118 that a phenomenon of oral tolerance exists and that clinical trials are underway involving the induction of oral tolerance. Goodnow does not support an allegation that oral tolerance does not work. Goodnow nether provides nor cites empirical data that convincingly refutes that oral tolerance is achievable. Rather, Goodnow supports the proposition that oral tolerance is achievable.

The Office has alleged that international application publication WO 02/053092 ("the '092 publication") teaches that "oral tolerance is fraught with numerous obstacles." In fact, the '092 publication actually demonstrates that tolerance can be accomplished and furthermore "oral and mucosal tolerance for the suppression and prevention of inflammatory conditions is well known in the art. Examples of candidate conditions, antigens and modes of therapy, can be found." WO 02/053092, at page 22, lines 25-27.

Indeed, the fact of the phenomena that underlies and enables the claimed methods is never denied in any publication cited by the Office. At most, the documents cited by the Office demonstrate that varying treatment parameters provides varying effectiveness. Experimentation to optimize treatment parameters is not necessarily undue if the art typically engages in such experimentation. *See, e.g., In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l

Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985); *see also In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976); M.P.E.P. § 2164.01.

In view of all the evidence submitted (including the Declarations of Dr. Jevnikar), and the absence of credible proof of non-enablement, there is no reason to doubt that one skilled in the art could make and/or use the claimed invention without undue experimentation. The rejection under 35 U.S.C. § 112, first paragraph, should be overturned.

Rejection under 35 U.S.C. § 103

Claims 52, 59-61, 63, 69-91 and 95 have been rejected under 35 U.S.C. § 103 as allegedly unpatentable over PCT published application WO 92/07581 in view of U.S. Patent No. 5,484,719 ("the '719 patent").

The prior art fails to establish a proper prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

The cited art fails to teach every element of the claimed invention. WO 92/07581 teaches a method for suppressing an immune response by administering cell extracts from donor tissue. Nowhere in the WO 92/07581 publication is it suggested that oral administration of a transgenic plant is an alternative method of suppressing an immune response. The '719 patent does not cure the deficiencies of WO 92/07581, because the '719 patent also fails to disclose oral administration of plants for suppression of an immune response.

One skilled in the art would not be motivated to combine and modify these two references, because the objectives of the two references are diametrically opposed and combining the references

as proposed would change the principle of operation of the '719 patent. The objective of the '719 patent is the opposite of the objective of the present application. The '719 patent teaches that expression of antigens from viral, bacterial or fungal antigens in a plant for a method of oral vaccination will have the effect of increasing the immune response. The present application is directed to the induction of oral tolerance with tolerogenic antigens with the object of suppressing an immune response.

If oral ingestion were to induce tolerance to the viral, bacterial or fungal antigens of the '719 patent, it would be the opposite of the desired effect. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 U.S.P.Q. 349 (CCPA 1959).

The combination of references fails to teach every element of the claimed invention. Moreover, as a matter of law, there would have been no motivation to modify and combine the cited references. For at least these reasons, the proposed combination fails to support a *prima facie* case of obviousness. The rejection of claims 52, 59-61, 63, 69-91 and 95 under 35 U.S.C. § 103 should be overturned.

Respectfully submitted,

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Appendix A
Appealed Claims

52. (Previously Presented) A method for suppressing or reducing the immune response of a mammal to an antigen comprising:

orally or enterally administering to the mammal an effective immune suppressive dose of a plant tissue or a partially purified plant tissue extract containing said antigen or an immunosuppressive fragment thereof, said plant tissue or partially purified plant tissue extract being obtained from a transgenic plant expressing said antigen or immunosuppressive fragment thereof.

59. (Previously Presented) The method of claim 52, wherein the plant tissue or partially purified plant tissue extract is selected from the group consisting of at least one plant part, an extract of total plant protein, and a partially purified plant protein preparation.

60. (Previously Presented) The method of claim 52, wherein the plant tissue or partially purified plant tissue extract is from at least one plant part selected from the group consisting of leaves, stems, seeds and tubers.

61. (Previously Presented) The method of claim 52, wherein the transgenic plant is transformed with a DNA construct for transforming a plant, said construct comprising a Cauliflower Mosaic Virus Ehn-35S promoter operably linked to a DNA coding sequence and further comprising a termination sequence in proper reading frame with the DNA coding sequence, wherein the termination sequence is a nopaline synthase termination sequence and the DNA coding sequence encodes the antigen.

63. (Previously Presented) A pharmaceutical composition for suppressing or reducing the immune response of a mammal to an antigen comprising:

an oral or enteral dosage form comprising an effective immunosuppressive dose of a plant tissue or partially purified plant tissue extract containing said antigen or an immunosuppressive fragment thereof and a pharmaceutically acceptable carrier, said plant tissue or partially purified plant tissue extract being obtained from a transgenic plant expressing said antigen or immunosuppressive fragment thereof.

69. (Previously Presented) The composition of claim 63, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola and low alkaloid tobacco.

70. (Previously Presented) The composition of claim 63, wherein the plant tissue or partially purified plant tissue extract is from at least one plant part selected from the group consisting of leaves, stems, seeds and tubers.

71. (Previously Presented) The composition of claim 63, wherein the transgenic plant is transformed with a DNA construct for transforming a plant, said construct comprising a Cauliflower Mosaic Virus Ehn-35S promoter operably linked to a DNA coding sequence and further comprising a termination sequence in proper reading frame with the DNA coding sequence, wherein the termination sequence is a nopaline synthase termination sequence and the DNA coding sequence encodes the antigen.

72. (Previously Presented) The method of claim 52, wherein the antigen is a mammalian transplantation antigen.

73. (Previously Presented) The method of claim 72, wherein the transplantation antigen is a human Major Histocompatibility Complex (MHC) protein.

74. (Previously Presented) The method of claim 73, wherein the MHC protein is selected from the group consisting of an MHC class I protein, an MHC class II protein, an MHC class II_ chain and an MHC class II_ chain.

75. (Previously Presented) The method of claim 72, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola and low alkaloid tobacco.

76. (Previously Presented) The method of claim 72, wherein the plant tissue or partially purified plant tissue extract is from at least one plant part selected from the group consisting of leaves, stems, seeds and tubers.

77. (Previously Presented) The method of claim 72, wherein the mammal is a human.

78. (Previously Presented) The composition of claim 63, wherein the antigen is a mammalian transplantation antigen.

79. (Previously Presented) The composition of claim 78, wherein the transplantation antigen is a human Major Histocompatibility Complex (MHC) protein.

80. (Previously Presented) The composition of claim 78, wherein the MHC protein is selected from the group consisting of an MHC class I protein, an MHC class II protein, an MHC class II_ chain and an MHC class II_ chain.

81. (Previously Presented) The composition of claim 78, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola and low alkaloid tobacco.

82. (Previously Presented) The composition of claim 78, wherein the plant tissue or partially purified plant tissue extract is from at least one plant part selected from the group consisting of leaves, stems, seeds and tubers.

83. (Previously Presented) The composition of claim 78, wherein the mammal is a human.

84. (Previously Presented) A method for suppressing the rejection of engrafted donor tissue in a recipient mammal comprising orally or enterally administering to the mammal an effective immunosuppressive dose of a plant tissue or a partially purified plant tissue extract containing a transplantation antigen of said donor tissue or an immunosuppressive fragment thereof, said plant tissue or partially purified plant tissue

extract being obtained from a transgenic plant expressing said transplantation antigen or immunosuppressive fragment thereof.

85. (Previously Presented) The method of claim 84, wherein the transplantation antigen is an MHC protein.

86. (Previously Presented) The method of claim 85, wherein the MHC protein is selected from the group consisting of an MHC class I protein, an MHC class II protein, an MHC class II_ chain and an MHC class II_ chain.

87. (Previously Presented) The method of claim 84, wherein the transgenic plant is selected from the group consisting of potato, tomato, alfalfa, canola and low alkaloid tobacco.

88. (Previously Presented) A transgenic plant comprising a plant expressing a recombinant mammalian transplantation antigen.

89. (Previously Presented) The transgenic plant of claim 88, wherein the transplantation antigen is a human Major Histocompatibility Complex (MHC) protein.

90. (Previously Presented) The transgenic plant of claim 89, wherein the MHC protein is selected from the group consisting of an MHC class I protein, an MHC class II protein, an MHC class II_ chain and an MHC class II_ chain.

91. (Previously Presented) The transgenic plant of claim 88, wherein the plant is selected from the group consisting of potato, tomato, alfalfa, canola, and low alkaloid tobacco.

95. (Previously Presented) An edible plant material comprising a plant tissue or partially purified plant tissue extract obtained from a transgenic plant of claim 88.